UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,567	08/24/2005	Pascal Furet	ON/4-32572A	5275

1095 7590 09/21/2007

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
09/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,567	FURET ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20060501*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-11 and 13-14 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-7, 10-11 and 13-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of formula I wherein the substituents R_1 and Z represent the independent substituent groups as defined in the claims, does not reasonably provide enablement for compounds of formula I wherein two vicinal R_1 substituents together or two vicinal Z substituents together with the carbon atoms of the phenyl ring (to which the substituents R_1 or Z are attached) form a heterocyclic ring. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the

above noted factual considerations.

The specification fails to enable the preparation of the entire scope of the claimed compounds. The process schemes in pages 15-25 of the specification, followed by the examples provide the essential starting materials to prepare the claimed compounds of formula I. All the examples disclose compounds wherein R_1 and Z represent the independent substituent groups, however, there is no disclosure of the sources of starting materials needed to prepare the compounds of formula I wherein two vicinal R_1 substituents together or two vicinal Z substituents together with the carbon atoms of the phenyl ring (to which the substituents R_1 or Z are attached) form a heterocyclic ring. The specification does not provide any explanation or sources of starting materials or the resulting products wherein two vicinal R_1 substituents together or two vicinal Z substituents together with the carbon atoms of the phenyl ring (to which the substituents R_1 or Z are attached) form a heterocyclic ring, such that a person of ordinary skill could determine which groups are suitable to prepare the instantly claimed compounds. For example, if one R_1 represents a group akyl-sulfonyl and another represents amino-sulfonyl, then a cyclic group formed by the two R_1 groups together will have completely different structural features, which are not described in the schemes nor in the examples. The resulting compounds will have a different structural nucleus than that of formula I. In view of the lack of direction provided in the specification regarding starting materials, the lack of working examples and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention. The starting material sources necessary to obtain the instant compounds must have been available as of the filing date in order to provide an enabling disclosure. See *In re*

Howarth, 654 F.2d 103, 210 USPQ 689 (CCPA 1981); *Ex parte Moersch*, 104 USPQ 122 (POBA 1954). Applicants should show that the sources of these starting materials was common knowledge or readily available at the time of filing.

2. Claim 13 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the treatment of non-small cell lung carcinoma, does not reasonably provide enablement for a method for the treatment of a disease which responds to an inhibition of protein tyrosine kinase generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claim 13 is drawn to 'a method for the treatment of a disease which responds to an inhibition of protein tyrosine kinase' and the specification provides EGFR, ErbB-2, KDR, etc. as examples of the protein tyrosine kinases. The specification provides sources of certain kinases (e.g., EGF-R, KDR) and assays to test the activity of the compounds with respect to

those kinases, however, does not provide any test procedures to measure the protein kinase inhibition activity in general. The specification merely recites that the compounds are useful as protein kinase inhibitors and based on the kinase inhibition activity, the specification provides that the compounds are useful in the treatment of proliferative disorders. The disclosure further provides a non-small cell lung cancer, squameous carcinoma, breast, gastric, ovarian, colon and prostate cancers, etc. as examples of proliferative disorders. The instant claim appears to be a 'reach through' claim. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification thereby requiring undue experimentation for one of skill in the art to practice the invention.

The specification does not provide any guidance to test the instantly claimed 'protein tyrosine kinase inhibition' activity generally. The recitation "protein tyrosine kinase" encompasses all members of the protein kinase super family. The specification does not provide the sources for the various enzymes encompassed by the instant claims, e.g., VEGF, KDR, EGFR, etc. The test procedures and data provided in the specification is with respect to the in vitro activity of the compounds in the inhibition of HER-1, HER-2 and KDR (see Example 129). Applicant did not state on record or provide any guidance regarding which state of the art assays may provide basis for the instantly claimed activity of inhibition of protein tyrosine kinase generally. Further, there is no disclosure regarding how this potential inhibitory activity is correlated to the clinical efficacy of the treatment of various disorders of the claims. As can be seen from specification pages 26-27, data related to the protein tyrosine kinase inhibition holds

significant role in determining the dosage regimen based on the minimal effective concentration of each of the compound to achieve the desired inhibition of the protein tyrosine kinases.

The instant claims are drawn to "a method for the treatment of a disease which responds to an inhibition of protein tyrosine kinase" which diseases include, for example, proliferative disorders. First, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The use disclosed in the specification is as protein tyrosine kinase inhibitors, in the treatment of a large list of proliferative diseases, which include non-small cell lung cancer, squameous carcinoma, breast, gastric, ovarian, colon and prostate cancers, etc. There are no test assays and procedures provided in the specification and there is nothing in the disclosure regarding how this recited activity correlates to the treatment of the diverse disorders encompassed by the instant claims. The diseases and disorders encompassed by the instant claims include various types of cancer, some of which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, as evidenced by the wide range of results obtained for the tested compounds. It is inconceivable as to how the claimed compounds can treat the large list of diseases embraced by the claims, which diseases respond to inhibition of protein tyrosine kinases

generally. Further, there is no disclosure regarding how the patient in need of the treatment requiring the specific kinase (i.e., VEGFR, KDR, EGFR, etc.) inhibiting activity is identified and further, how all types of the diseases having divers mechanisms are treated. The state of the art is indicative of the unpredictability of the therapeutic approach based on kinase inhibiting activity. Cressey et al. (Medline Abstract 2005) state that "Although numerous publications dealing with the measurement of circulating VEGF for diagnostic and therapeutic monitoring have been published, the relationship between the production of tissue VEGF and its concentration in blood is still unclear".

According to the specification, the instant claims include 'a method for the treatment of proliferative disorders' which include various types of cancers (see pages 6-7). The terms 'cancer' and 'proliferative disorders' represent anything that is caused by abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. For example, Yano et al. (Medline Abstract 2000) provides for the treatment of malignant pleural effusion of human lung adenocarcinoma by inhibition of VEGF receptor, however, the state of the art is not indicative any pharmaceutical agents that are useful in the treatment of cancer generally. Cecil Textbook of Medicine states

that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. In reference to cancer treatment using protein tyrosine kinase inhibitors, Traxler (Exp. Opin. Ther. Patents, 1997) stated that "pharmacological properties such as stability in biological media, bioavailability, metabolism or formulability are significant hurdles" see page 585, col. 2, lines 33-36.

The diagnosis of each of the disease is generally suggested by medical history and reports of endoscopy, cytology, X-ray, biopsy, etc. depending on the symptoms, signs and complications, which is essential to establish the dosage regimen for appropriate treatment. The disclosure does not provide any guidance towards the dosage regimen required to facilitate the treatment and/or inhibition of the claimed disorders, nor indicate competent technical references in the appropriate methods.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Traxler, in a recent article (Exp. Opin. Ther. Patents, 1997) stated that "The

concept of the inhibition of growth factor receptor-mediated signal transduction via inhibition of its protein tyrosine kinase is a novel, **not yet proven** clinical approach to the regulation of cell proliferation", see page 585, col. 1. Therefore, the state of the art provides the need of undue experimentation for the instantly claimed therapeutic benefits.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

MPEP § 2164.01(a) states that "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)". That conclusion is clearly justified here and undue experimentation will be required to practice the claimed invention.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 provides for the use of the compound of claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

Claim 10 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an

> international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-7, 10-11 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Mueller et al., WO 03/049542 (filing date December 5, 2002). The instant claims read on reference disclosed compounds, see the structural formula (I) in page 1 and the corresponding compounds of Examples 3a and the compounds that correspond to formula 1.01 in Table 01.

Note: Applicant can not rely on foreign priority based on United Kingdom 0215844.2 (filed July 8, 2002) to overcome the rejection under 35 U.S.C..102(e) because the priority document does not fully support the instant claims. The structural formula in the priority document is different from the structural formula provided in the instant claims because the formula of the priority application does not include all of the structural limitations of the instant claims. For example, the structural formula in the priority application does not include R_3, (see pages 1-2 of the priority document).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 1-11 and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Armistead et al., WO 01/60816. The reference teaches a generic group of arylaminopyrimidine compounds that are structurally analogous to instantly claimed compounds. See the structural formula in page 4 and the corresponding species of compound 33 (page 28). The compounds are taught to be useful as kinase inhibitors useful as pharmaceutical therapeutic agents, see the abstract. The instant compounds differ from the reference compounds by having the pyrazolyl group attached at a position different from the reference compounds, i.e., at the 3-position as compared to the 1-position for reference compound and therefore, the instantly claimed compounds are positional isomers of the reference compounds. It would have been obvious to one having ordinary skill in the art at the time of the invention to prepare the instantly claimed compounds because they are positional isomers of the reference compounds. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such isomeric compounds are suggestive of one another and would be expected to share similar properties and therefore, the same use as taught for the reference compounds, i.e., as pharmaceutical agents. It has been held that a compound, which is structurally isomeric with a compound of prior art is prima facie obvious absent unexpected results. *In re Finley*, 81 USPQ

383 (CCPA 1949); *In re Norris*, 84 USPQ 458 (CCPA 1950); *In re Dillon*, 919 F.2d at 696, 16 USPQ2d at 1904 (Fed. Cir. 1990).

2. Claims 1-7, 10-11 and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anantanarayan et al., WO 00/31063. The reference teaches substituted pyrazolyl-pyrimidinyl compounds, see formula (IA) in page 4 and the compound of Example A-326 (page 355). The reference compounds are taught to be useful as pharmaceutical therapeutic agents, see pages 23-25. The instant claims exclude the reference disclosed compound, see the proviso statement, however, include compounds that either differ by a $-CH_2$ group (i.e., wherein any of the groups are substituted by a methyl, for example, compounds wherein R_1 is ethoxy). Therefore, the instantly claimed compounds differ from the reference compounds by being structural homologs. It would have been obvious to one having ordinary skill in the art at the time of the invention to modify the reference compounds to prepare the structural homolog. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally analogous compounds are expected to possess similar properties. It has been held that compounds that are structurally analogous to prior art compounds are *prima facie* obvious, absent a showing of unexpected results. *In re Hass*, 60 USPQ 544 (CCPA 1944); *In re Henze*, 85 USPQ 261 (CCPA 1950).

Duplicate claims

Applicant is advised that should claim 1 be found allowable, claim 10 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 10 recites the intended use for the compounds of claim 1 and does not contain any structural distinction from claim 1.

Receipt is acknowledged of the Information Disclosure Statement filed on May 1, 2006 and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Deepak Rao/
Primary Examiner
Art Unit 1624

September 16, 2007